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Review

Is there a role of coral bone substitutes in bone repair?

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ABSTRACT

Xenogeneic bone graft materials are an alternative to autologous bone grafting. Among such implants, coralline-derived bone grafts substitutes have a long track record as safe, biocompatible and osteoconductive graft materials. In this review, we present the available literature surrounding their use with special focus on the commercially available graft materials. Corals thanks to their chemical and structural characteristics similar to those of the human cancellous bone have shown great potential but clinical data presented to date is ambiguous with both positive and negative outcomes reported. Correct formulation and design of the graft to ensure adequate osteo-activity and resorption appear intrinsic to a successful outcome.

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Introduction

Bone grafting is the most common transplant procedure performed today. It is estimated that approximately 450,000 bone transplantation procedures are performed annually in the USA and 2.2 million worldwide [1]. Autologous bone grafting has all the properties of the ideal graft material, being an osteoinductive and osteoconductive scaffold with no immunogenicity and containing significant numbers of osteoprogenitor cells [2,3]. However, its use has several drawbacks including limited availability, variable graft quality, increased operative time and donor site morbidity [4]. To overcome the increasing need for bone graft materials, research has focused on the development of novel bone graft substitutes [5,6]. A large number of substitutes have been developed and a significant number are commercially available for clinical use.

Bone graft biomaterials derived from mineralizing marine organisms have been vividly investigated over the last 50 years. Several marine species produce mineralized structures within their anatomy that resembles the human bone [7]. Examples of such species include sponges (*Porifera*), red algae (*Rhadophyta*), corals (*Cnidarians*) and a range of other organisms like snails (*Mollusca*), starfish (*Echinodermata*) etc [7]. Among such marine derived biomaterials, corals are one of the most studied in the field of bone tissue engineering. The aim of the herein manuscript is to present the available literature on coral bone substitutes.

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Corals as graft material

Corals are marine invertebrates belonging in the class *Anthozoa* of phylum *Cnidaria*. They are approximately 7 thousand species and can be classified as soft corals (without an inorganic structure) and hard corals or stony corals. The hard corals typically live in compact colonies of many identical individual polyps. The polyps reside in a centripetal exoskeleton. The outer layer of the corals is inhabited by calcicoblasts, which like the osteoblasts they produce a hard outer skeleton composed of calcium carbonate which, strengthens and protect the organism.

Studies on the coralline structure revealed significant similarities to that of cancellous bone [8]. The coralline material is characterized by a uniform network of interconnected channels and pores similar to those in osteon-evacuated bone grafts [8,9]. When implanted in-vivo was found to be biocompatible. It allowed vascular ingrowth and inhabitation of cell lineages found in bone. The new bone formation occurred without an intervening endochondral phase [8]. Resorption of the corals is carried out by osteoclastic activity and the actions of the carbonic anhydrase enzyme [10]. Resorption is linked to bone apposition and can be influenced by the systemic administration of acetazolamide, a diuretic inhibiting carbonic anhydrase [10,11]. Among the different coral species, significant structural differences exist. This could have direct implications to their bone forming capacity. It has been previously proposed that the larger the porosity volume, the greater was the coral resorption as well as the new bone apposition [12]. Three main species have been investigated as bone graft substitutes: *Acropora* sp., *Goniopora* sp., and *Porites* sp. *Porites* sp. have a homogeneous structure and consistent pore size while *Goniopora* sp. have a bimodal pore size and a strongly disordered structure [12,13]. *Acropora* has oriented pores, irregular pore size and the largest permeability compared to *Goniopora* and *Porites* sp. [13]. Their transverse section however, was closed and the useful size was limited because of its habitat type [13]. *Porites* had the smallest pore size and had the lowest permeability. Other coral genera have been previously investigated but with very limited use [14–16]. Among them, *Dichocoenia stokes* were found to trigger a foreign-body reaction when implanted in rabbits [14]. These corals were also found to have slow resorption rates [15]. *Facites* and *Lobophyllia* and *Pocillopora* have a skeletal structure similar to the diaphysis of compact bone with a dense and compact outer wall (theca) surrounded by a thin inner septa (closed porosity) [16,17]. Other coral genera exist like the *Montipora*, *Fungia*, *Polyphyllia*, *Acanthastrea*, and *Turbinaria* but our current available evidence on these corals is rather poor or non-existent.

In the early 70s, observations suggesting that porous structures have improved bone integration sparkled a race towards the ideal bone graft substitute [18]. The foundations of stony corals as biomaterials have been set a few years later by the work of White et al. [19] proposed the replamineform technique (replicated life forms) which could be used to duplicate the coral carbonate microstructure and convert it to ceramic, metal, or polymer materials. Utilizing this technique the unique coral pore structures composed of the brittle calcium carbonate could be preserved and copied to produce an alternative material with the same structure but converted to hydroxyapatite. In addition to the converted form, corals have been used in their natural form i.e. as calcium carbonate. The bone formation of both calcium carbonate and hydroxyapatite occurred initially on surface of the pore regions and progressed toward the center of the pore and was linked to graft resoption [20]. At present there are two commercially available corals: the Biocoral® composed of corals on their natural form and Pro Osteon™ composed of coralline material converted to hydroxyapatite.

Experimental studies

In-vitro studies

The vast majority of the available in-vitro studies have analysed the biocompatibility between the corals and the osteoprogenitor cells. Scaffolds derived from corals should be able to support the attachment, proliferation and differentiation of Mesenchymal Stem Cells (MSCs) and osteoblasts [21]. The available studies showed that the corals are not cytotoxic and promote cell growth [22]. When cells were seeded on coral granules revealed good attachment, spread, and proliferation on the material surface [23]. Comparing cryopreserved bone allograft, coralline hydroxyapatite and demineralized freeze-dried dentin revealed that coralline hydroxyapatite was the most potent promoter of the long term cellular attachment [24]. In a similar study including commercially available graft products, Doherty et al. compared the levels of cellular attachment of rat bone, Surgibone®, Ostilit®, Biocoral® and Tisseel® [25]. The results showed that rat bone and Tisseel® (fibrin glue) had the greatest cell affinity followed by Biocoral® and Surgibone®, while Ostilit® did not facilitate cellular attachment.

Following osteogenic induction, mineralized matrix and alkaline phosphatase activity was noted within the coral particles [23,26]. DNA content, ALP activity, Ca content were significantly higher in osteoblasts seeded in coral scaffold in comparison to other materials [26]. Mineralized nodules formation (both in area and number) was more predominant on the coral surface than in glass disk [26]. Gene expression analysis of osteoblasts loaded on coral *Porites* sp. scaffolds showed an increased expression of the RUNX2, osteopontin, alkaline phosphatase and osteocalcin genes. The authors concluded that coral is a favourable carrier for osteogenetically competent cells to attach and remain viable [27]. In another study significantly higher levels of osteogenic differentiation markers, namely alkaline phosphatase (ALP), Osteocalcin (OC) levels, and Osteonectin and Runx2, Integrin gene expression were detected in the cultures on corals (*Porites* sp) in comparison to bone [28].

A number of authors have tried to expand corals properties with the addition of an osteoinductive element. Coral particles are capable to absorb and subsequent elute transforming growth factor beta 1 (TGF-beta1) in vitro [29–31]. TGF-beta1 release was also found to vary with particle size, higher release being obtained with the smaller particles [29]. In a study by Zhang et al. a coral/chitosan composite was combined with a plasmid encoding platelet-derived growth factor B (PDGF-B) gene. The resulted scaffold found to upregulate the proliferation and the PDGF-B expression of the seeded cells [30]. Combinations of platelet-rich plasma (PRP), marrow stromal cells (MSCs) and porous coral have shown to exert a higher osteogenic effect [31].

Animal studies

The available evidence based on experimental animal studies which explore the potential of coralline grafts to support bone healing can be subdivided in three distinct methodologies; studies where the coralline grafts have been implanted in ectopic places, studies where coralline material implanted on bone in cases of fracture healing or bony defects site and finally composite coralline grafts preloaded with growth factors in applications including bone defects spinal fusion.

Ectopically implanted coral material seem to be biocompatible but inner without inducing an osteogenic response [32]. Once an osteoinducing signal is added either in the form of osteogenic cells or growth factors, bone formation is initiated [32–34]. The structural characteristics and the degree of bone formation was